Update / Le point

Public health impact of schistosomiasis: disease and mortality*

WHO Expert Committee on the Control of Schistosomiasis[1]

The public health significance of schistosomiasis is often underestimated for two reasons. First, like all helminthic infections, the distribution of worms in any community is widespread but uneven, i.e., few have heavy infections and severe disease, while many have lighter infections and fewer symptoms. Some people with very few worms may have no symptoms. Secondly, severe disease usually follows after many years of silent or mildly symptomatic infection. Even if only 10% of those 200 million infected with schistosomiasis have severe clinical disease, this still represents 20 million seriously ill people. Of the remaining 180 million infected people, an estimated 50–60% also have symptoms—a public health problem of enormous proportions. The impact on public health can be assessed in terms of the frequency and severity of schistosomiasis-related disease, incapacity and premature death.

This article presents extracts from the Expert Committee's recently published second report and deals with morbidity and mortality, as well as the links between schistosomiasis and cancer, nutrition and intercurrent infections, and the immune response to schistosomiasis.

Schistosomiasis is caused by any of five species of trematode parasite. Each species may give rise to acute or chronic disease with widely differing symptoms and clinical signs (*1*). Since the advent of safe and effective chemotherapy, clinicians have recognized an improvement in the general health of treated patients, even when specific signs or symptoms of the disease were not evident before treatment. A thorough understanding by health workers of the disease patterns of schistosomiasis and of the beneficial effects of treatment will facilitate diagnosis and improve the quality of reporting as control progresses.

Morbidity

Recent studies of morbidity caused by chronic schistosomiasis have confirmed a general relationship between the intensity of infection and high morbidity in children (*1*). In communities with a high prevalence and intensity of infection there is a wide range of clinical manifestations. Until recently, physical examination and laboratory investigation were the standard diagnostic techniques. The recent introduction of portable ultrasonography equipment that can be used in the field—at village level if required—should enable diagnosis to be made with greater accuracy and sensitivity in the future.

Schistosoma haematobium

Infection with *S. haematobium* is associated with very high morbidity. Up to 50–70% of infected individuals in any endemic locality have symptomatic urinary tract findings including haematuria, dysuria or frequency. The severity of the disease depends mainly on the intensity of infection. A high proportion of moderately or heavily infected patients, particularly children, have considerable damage of the urinary tract, sometimes leading to obstructive uropathy.

The acute granulomatous response to parasite eggs in the early stages causes urinary tract disease, such as urothelial ulceration and bladder polyposis. By contrast, in chronic disease, usually in older patients, ureteric and bladder fibrosis and calcification are more common. In the early stage, the inten-

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sity of infection usually reflects the severity of the disease. In the late stage, urinary egg count is less related to the severity of the disease, and morbidity can be better assessed by laboratory investigations, radiography and ultrasound.

Hospital radiological evaluation of urinary schistosomiasis includes a plain abdominal X-ray, intravenous urography, and retrograde cystography and pyelography. Typical lesions demonstrated radiologically are hydronephrosis, hydroureter, ureteric stricture, dilatation or distortion, ureteric calcification, polyps, ureterolithiasis, calcified bladder, bladder filling defect caused by granuloma, polyps or carcinoma, reduction in bladder capacity, irregular contraction of the bladder wall or dilated bladder due to bladder neck fibrosis. In general, more urinary tract disease is seen radiologically in communities with a high intensity of infection in children. Some of the urinary tract lesions in children may be reversed by treatment; in adults, the more severe changes, with bladder calcification, may not regress.

A major advance in the understanding of the natural history of *S. haematobium*-related urinary tract morbidity has come through the introduction of the portable ultrasound machines for non-invasive examination of the kidneys and bladder. In studies from different geographical areas, results of ultrasound studies have correlated well with findings from intravenous urography and cystoscopy.

Renography can be used to assess the function of each kidney and detect obstruction of the urinary tract, especially in children. Following treatment in children, the renogram is restored to normal more quickly than the pyelogram, which may still show structural damage. Although computed tomography (CT) can clearly demonstrate calcification of the urinary tract, such hospital-based investigations, including renography, have a limited role in monitoring morbidity control within the community.

Schistosoma japonicum *and* Schistosoma mekongi

Acute clinical disease, or Katayama fever, following penetration of the cercaria, is characterized by organomegaly, fever and eosinophilia. It is usually seen either in people living in an endemic area at the time of their first exposure or in uninfected people who enter an endemic area for the first time. Patients with active chronic infection or with a history of infection and antischistosomal treatment may occasionally present with acute symptoms due to massive exposure to cercariae over a short period.

In most people with chronic schistosomiasis the disease is subclinical. The main symptoms are weakness, abdominal pain, irregular bowel movement and blood in the stools. By palpation the liver is smooth and enlarged, but in severe cases may be nodular or irregular. Splenomegaly is frequent, especially in the late stage or in heavy infection. Patients with gross splenomegaly often have hypersplenism. Advanced hepatosplenic disease is usually associated with dilatation of abdominal collateral veins, gastro-oesophageal varices and eventually ascites.

In intestinal schistosomiasis liver function usually remains normal, but in patients with hepatic disease there is often some functional impairment. The decrease in serum albumin and the increase in immunoglobulin concentration are usually well demonstrated by serum electrophoresis. When viral hepatitis B and *S. japonicum* infection occur together, there is higher morbidity and mortality than would be caused by either infection alone.

In adult hospital patients with schistosomiasis, cerebral schistosomiasis occurs in 1.7–4.3%. The acute form presents as a meningoencephalitic syndrome. In the chronic phase, Jacksonian convulsions and grand mal seizures, with permanent electroencephalographic changes are most frequent, while psychomotor and autonomic seizures are rarely seen.

Ultrasound evaluation of *S. japonicum* morbidity is currently in progress in China and in the Philippines and preliminary findings suggest that this technique is as good as or more effective than surgical biopsy in evaluating the presence and degree of portal fibrosis before treating a patient. A similar success in evaluation is reported for *S. mansoni*.

The clinical manifestations of *S. mekongi* infection are similar to those of *S. japonicum*. Morbidity due to *S. mekongi* alone is difficult to distinguish from that due to other parasitic infections in the same endemic areas, especially *Opisthorchis viverrini*. Hepatomegaly and splenomegaly due to other causes are very common in endemic areas.

Schistosoma mansoni

The main impact on public health is due to chronic infection leading to intestinal and hepatosplenic involvement. In areas of low prevalence severe clinical features are seen in a relatively small proportion of patients. Symptoms such as abdominal pain, bloody diarrhoea and fatigue are reported by infected people in high-prevalence localities.

The principal intestinal lesions of *S. mansoni* infection are colonic polyposis (especially in Egypt), focal fibrosis, and inflammation. Schistosomal polyposis is directly related to the intensity of infection. Within the polyps the concentration of *S. mansoni* eggs is much higher than elsewhere in the intestine. Polyps are inflammatory and not adenomatous.

Hepatosplenic involvement is the most important cause of morbidity in *S. mansoni* infection.

Hepatic fibrosis and portal hypertension may be life-threatening and are irreversible in advanced disease. In endemic communities, hepatomegaly in childhood has been correlated with intensity of infection. Patients with intestinal symptoms may remain otherwise asymptomatic until the disease is well advanced or haematemesis occurs. In the early stages, the left hepatic lobe is predominantly enlarged. In the late stages, the size of the liver may decrease and ascites may develop due to portal hypertension and hypoalbuminaemia. Haemorrhage from gastro-oesophageal varices is often caused by schistosomal hepatic fibrosis. Hepatocellular failure may be life-threatening, especially if there is concomitant viral infection. In some patients with hepatosplenic *S. mansoni* infection nephrotic syndrome due to immune-complex glomerulonephritis may develop.

Ultrasonography can demonstrate the characteristic schistosomal portal fibrosis as well as the dilatation and patency of portal and splenic veins, and can clearly differentiate schistosomal fibrosis from post-hepatitic cirrhosis (*2*). Excellent sensitivity and specificity have been shown for ultrasonography compared with hepatic wedge biopsy in the diagnosis of schistosomal hepatic fibrosis. Since ultrasonography equipment is portable, clinical epidemiological studies can be carried out using the technique within the community. Community-based ultrasound monitoring of morbidity due to *S. mansoni* infection is still scarce. Guidelines are available for evaluating the application of ultrasound in schistosomiasis morbidity surveys.[a]

Schistosoma intercalatum

Compared with other schistosomes that infect humans, less is known about infection with *S. intercalatum* from west and central Africa but it is considered to be the least pathogenic. Differences between the Cameroon and Zaire strains of *S. intercalatum* need to be better defined before any conclusions are drawn about their pathogenicity.

The highest prevalence and intensity of infection occur between the ages of 5 and 14 years. The intensity of infection tends to decrease with age, and people over 45 years of age are rarely infected. The main clinical manifestations of disease due to *S. intercalatum* infection are lower abdominal pain and dysentery.

There is a positive association between the intensity of infection, assessed by stool egg count, and symptoms of diarrhoea and blood in the stool. As with other schistosomal infections, *S. intercalatum* may be associated with severe *Salmonella* infections. Lesions of the intestine are limited to the rectum and sigmoid colon. Egg granulomas are occasionally seen in the portal area of the liver. Left-lobe liver enlargement is associated with heavy infections. Liver fibrosis and portal hypertension have not been seen.

Schistosomiasis and cancer

While associations between schistosomiasis and several cancers exist, epidemiological evidence suggests that schistosomes are probably co-carcinogens. On the other hand, there is experimental evidence for *S. haematobium*-associated carcinoma of the bladder in non-human primates.

An increased incidence of squamous cell carcinoma of the bladder has been reported in many areas endemic for *S. haematobium* infection. Supporting data have been reported from Egypt, Iraq, Kuwait, Malawi, and elsewhere, and confirmed in case-control studies from Zambia and Zimbabwe. Individuals with concurrent schistosomiasis develop malignancy at a lower mean age than do non-infected cohorts. In these areas, squamous cell carcinoma of the bladder is more frequent than transitional cell tumours, accounting for 44–82% of the total, whereas the opposite is observed when schistosomiasis is not endemic.

Although the mechanism of carcinogenesis in the urinary bladder is unknown, there is evidence that early treatment of schistosomiasis is a primary preventive measure. Such intervention will lower the risk of carcinogenesis that is directly (if immune-mediated) or indirectly (if due to increased urinary carcinogen exposure secondary to bladder outlet obstruction) related to the infection by allowing early lesions to heal or by reducing the risk of their development. Cancer registry surveillance is recommended to confirm these effects.

Although colorectal cancer has been associated with *S. japonicum* infection, there is little experimental or epidemiological evidence to confirm a predisposing role for schistosomiasis. A nationwide retrospective survey of cancer in China, between 1973 and 1975, showed that cancer of the large intestine was seen mainly in areas with a high prevalence of schistosomiasis. The National Cooperative Group on Pathology and Prognosis of Colorectal Cancer in China reported that the five-year survival rate of patients with colorectal cancer complicated by schistosomiasis was significantly lower than in patients without schistosomiasis.

[a] *Meeting on ultrasonography in schistosomiasis: proposal for a practical guide to the standardized use of ultrasound in the assessment of pathological changes.* Unpublished WHO document, TDR/SCH/ULTRASON/91.3 & CTD/91.3, 1991.

There is no proven link between schistosomiasis and hepatic and gastric carcinoma. However, in Brazil and Egypt, splenic lymphoma and schistosomiasis have been observed to occur concurrently.

Schistosomiasis and nutrition

S. haematobium infection is associated with anaemia, and probably causes or aggravates anaemia in the presence of low dietary iron, hookworm infection or malaria (*3*). In Africa, urinary schistosomiasis is associated with low weight for height in both children and adults. The disease can inhibit growth in children, but the growth rate improves after successful treatment. Further studies are needed to determine the effect of urinary schistosomiasis on children's school attendance and performance, and on the work capacity and productivity of both children and adults.

S. mansoni and *S. japonicum* infections cause intestinal blood loss. However, the magnitude of this loss over time and its effect on nutritional status, anaemia, growth and physical fitness remain unclear. In addition, the contribution of treatment of schistosomiasis in improving nutritional status has not been assessed. Growth retardation due to severe *S. mansoni* or *S. japonicum* infection can be reversed by treatment.

Schistosomiasis and intercurrent infections

Viral hepatitis

In hospital patients from Egypt, Kuwait, Malawi and the Sudan, hepatitis B virus (HBV) antigenaemia has been significantly more common in *S. mansoni*-infected patients, particularly those with hepatosplenic schistosomiasis, than in uninfected controls. In Egypt, *S. mansoni* infection has been significantly more frequently associated with the presence of hepatitis B surface antigen (HBsAg) and anti-hepatitis B antibody (anti-HB) than has *S. haematobium* infection. However, in most population-based studies, this association has not been found, because of high frequency of hepatitis B in the general population. These observations suggest that interaction between HBV and *S. mansoni* infection causes serious liver disease and that people with both infections are more likely to be hospitalized.

Recent studies showing a decreased response to hepatitis B vaccine among children of mothers with schistosomiasis should be confirmed by further studies and follow-up in the large-scale vaccination programmes under way in endemic areas. Hepatitis B vaccination protects against hepatocellular carcinoma and may diminish the severity of liver disease in patients with schistosomiasis.

Higher morbidity and mortality are seen with combined HBV and *S. japonicum* infection than with either infection alone. As in the case of *S. mansoni* and HBV, clinical and pathological studies have confirmed the association but population studies have not.

Bacterial infections

The frequent association of *Salmonella* spp. with schistosome infection and complete cure after treatment of schistosomiasis have long been recognized. The bacteria are found in the tegument or in the intestinal tract of *S. haematobium* and *S. mansoni* adult worms. These concomitant infections are characterized by prolonged fever, significant hepatosplenomegaly, eosinophilia, with or without leukocytosis, and persistently positive blood cultures for salmonellae. Effective treatment of schistosomiasis may eliminate both infections, although antibiotic treatment may also be required for the bacterial infection.

Other concomitant bacterial infections such as *Escherichia coli* may cause important complications in hepatosplenic disease due to *S. mansoni* and in obstructive renal disease due to *S. haematobium*.

Human immunodeficiency virus (HIV)

Thus far, reports of the association of schistosomiasis and HIV infection have been infrequent. The recent discovery of immunological cross-reactivity between an HIV-1 virion infectivity factor (vif) and a surface antigen of *S. mansoni* lends support to the hypothesis that schistosomiasis, which also produces marked alterations of immune function, could alter a patient's vulnerability to HIV and vice versa.

People with simultaneous *S. mansoni* and HIV infections form few granulomas around *S. mansoni* eggs. However, persons with terminal AIDS and those positive for HIV-1 antibodies who are infected with *S. mansoni* have been reported to develop antibodies to *S. mansoni* egg antigens.

Immune response to schistosomiasis

Immune responses in schistosomiasis are related both to the development of resistance to reinfection and to a granulomatous reaction around schistosome eggs. Epidemiological studies in different endemic areas indicate that the prevalence and intensity of schistosome infection rise during the first 15 years of

life, followed by a decline suggesting a gradual diminution of infection coupled with the development of resistance.

In Kenya, following treatment of *S. mansoni* infection, both susceptible and resistant children demonstrate high levels of IgG antibodies that can mediate eosinophil-dependent damage to schistosomula *in vitro*, but blocking antibodies, including some IgM and IgG isotypes, prevent the expression of immunity in the susceptible group of children. In the Gambia, protective immunity increasing with age against *S. haematobium* infection has been seen. Observations on reinfection after treatment in the Gambia (*S. haematobium*), in Brazil (*S. mansoni*) and in Egypt (*S. mansoni* areas) indicate that resistance may partly depend on IgE/IgG4 ratios, with IgE mediating resistance and high levels of IgG4 antibodies blocking these mechanisms in children. These studies, demonstrating that immunity in humans develops as age increases, give hope that it may be possible to develop a vaccine against the disease.

The immunological consequences in children of an infected mother are unknown, but the fact that children born in endemic areas may express a wide range of immune responses should be considered with regard to both morbidity studies and vaccine development.

The peripheral blood mononuclear cells of patients with early infection respond strongly to soluble egg antigen (SEA), while their response to adult worm antigens and cercarial antigens develops more slowly. As the infection becomes chronic, a reduced anti-SEA proliferative response and a greater response to adult worm antigens are seen. Antibody production in acute and early infection clearly differs from that observed in most chronically infected patients who have lower levels of IgM and IgG anti-schistosome antibodies. Acute and chronic schistosomiasis can be distinguished serologically on the basis of high specific IgM and/or IgA titres and high titres of anti-keyhole limpet haemocyanin (KLH) IgG in acute infections.

Immunoregulation in relation to granuloma formation in chronic schistosomiasis seems to be predominantly cellular, implicating a CD8+ T lymphocyte that is activated by a set of cytokine mediators. When treated with sera from patients with chronic schistosomiasis, lymphocytes from patients with active schistosome infections inhibit granuloma formation *in vitro*. Circulating immune complexes may regulate granulomatous hypersensitivity to *S. mansoni* eggs in patients with chronic schistosomiasis by inducing macrophages to secrete suppressive prostaglandins.

Mortality

Mortality from schistosomiasis has been poorly documented in most endemic countries, and death certificates and patients' records rarely identify schistosomiasis as the underlying cause of death. There is therefore, no doubt that mortality due to schistosomiasis continues to be underestimated, and improved data collection in health services is needed.

Annual mortality due to *S. haematobium* infection in East Africa has been estimated at 1 per 1000 infected adults. It has been estimated, however, that primary prevention by control of urinary schistosomiasis would reduce the global rate of carcinoma of the bladder by 5000–10 000 cases per year (*4*).

In 1984, the annual mortality due to schistosomiasis caused by *S. mansoni* in Brazil was estimated at 0.5 per 100 000 total population; at the same time in Suriname the figure was estimated to be 2.4 per 100 000 inhabitants. Before the introduction of praziquantel in China, severe acute schistosomiasis due to *S. japonicum* had a 2.5–20.7% mortality rate, and in Leyte (Philippines) the annual mortality among 135 untreated patients was 1.8%. The control of schistosomiasis through large-scale chemotherapy in Brazil was associated with a decline in annual mortality between 1977 and 1988, from 0.67 to 0.44 deaths per 100 000 inhabitants. It is expected that the more widespread use of current antischistosomal drugs for morbidity control in highly endemic areas will also reduce mortality. *S. intercalatum* infection has never been reported as a cause of death.

Conclusions

Strategy of control. In recognizing the achievements of control of morbidity due to schistosomiasis in the past seven years, the Committee endorsed greater flexibility to extend the objective of control. The success of the use of large-scale chemotherapy has revealed areas where the prevalence and intensity of infection were reduced less than had been expected. In areas of high prevalence, morbidity control remains the strategy of choice. If resources and an operational health care system permit, strategies for transmission control can also be envisaged in all areas.

Integration: a process. The Committee supported the concept that all health services, in particular the primary health care systems, and other sectors have integrated roles in the control of schistosomiasis. National commitment is required to adopt a strategy for control of schistosomiasis supported by a plan of action that defines the roles of all sectors.

Different types of schistosomiasis. Although the biological cycles may be similar, the epidemiology, clinical manifestations and response to treatment are distinct for each type of schistosomiasis. Thus a more critical approach to the strategies and approaches in 41 countries with more than one type of schistosomiasis was suggested.

Schoolchildren: a major target. The epidemiological distribution of prevalence and intensity of infection supports the Committee's concern that control programmes should give priority to school-age children, who are the fastest growing vulnerable group in developing countries. The harmful effects of schistosomiasis on growth, development and health status of this vulnerable age group are greater than was previously appreciated.

Health education. Health education remains a high priority in control programmes. A health education approach can be developed in all endemic countries, emphasizing personal hygiene and the people's role in schistosomiasis.

Safe water supplies. The International Safe Drinking Water Supply and Sanitation Decade has focused the attention of donors on the felt needs of developing countries endemic for schistosomiasis. This has benefited endemic areas and shown that closer coordination between schistosomiasis control and water supply and sanitation projects would assist in targeting areas with a high prevalence of the disease. Schistosomiasis control programmes are more sustainable in areas with water supply and sanitation programmes. The use of schistosomiasis rates as reliable indicators of the impact of water supplies on health is endorsed in all endemic countries.

Technology in the field. Advances in general and biomedical technology have been proved to contribute effectively to control. Microcomputers are taking their place in database management at central and peripheral levels. Ultrasound technology is progressing at such a rate that its use at the village level to assess morbidity and the impact of control is now feasible and provides an excellent opportunity for collaboration between curative and public health services. Health education through use of videotapes and television can reach villages with targeted messages.

Epidemiology. The Committee noted that the epidemiology of schistosomiasis is changing with the environment and unbalanced socioeconomic development. For the first time the Committee was asked to consider the basis for eradication and agreed that Japan and Montserrat had now achieved that status. The increase in S. mansoni in the deltas of the Nile, Senegal and Volta rivers after dam construction, the increase in urban schistosomiasis in north-east Brazil and in western and central Africa, and the resurgences of transmission in central China show that schistosomiasis remains a constant and undiminishing threat.

Water resources development. The Committee noted that health risk assessment was not consistently included in the terms of reference of pre-feasibility and feasibility studies for water resources projects. Budgeting and financing to implement appropriate intervention measures need to be coordinated with ministries of health and development agencies.

High costs. The cost of control remains high. The cost of praziquantel is a major constraint in achieving effective control of schistosomiasis, but this is only one of the costs of control. The diminishing per capita expenditures on health in developing countries should be of concern to the international community.

Long-term commitment. The strategy of control of schistosomiasis requires long-term commitment from the international to the local level. The increasing understanding of the disease, the proof of the effectiveness of available tools for diagnosis and treatment, the increasing capacity of health services, and the increasing emphasis on community involvement and management continue to augur well for progress in control of the disease.

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